Clinical Infectious Diseases
BRIEF REPORT

Doravirine Concentrations and Human Immunodeficiency Virus Type 1 RNA in the Genital Fluids of Virologically Suppressed Adults Switching to Doravirine Plus Emtricitabine/Tenofovir Alafenamide

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Doravirine (DOR) concentrations and HIV-1 RNA were evaluated in genital fluids from adults with HIV on stable therapy who switched to DOR + FTC/TAF. High protein-unbound DOR concentrations were observed in both seminal plasma and cervicovaginal fluid. DOR + FTC/TAF maintained viral suppression in genital fluids in all but 1 participant.

Keywords. HIV-1; antiretroviral therapy; doravirine; semen; cervicovaginal fluid.

Penetration of antiretroviral therapy (ART) in some tissues is limited by anatomical and physiological barriers, which may contribute to residual human immunodeficiency virus (HIV) replication and replenishment of the viral reservoir [1, 2]. These sanctuaries include both the male and the female genital tracts [1, 3].

In people with HIV (PWH) receiving ART, sexual transmission of HIV does not occur during unprotected sexual intercourse if an undetectable HIV plasma viral load is maintained [4], and mother-to-child transmission is prevented in females with suppressed plasma viral load receiving ART [5].

Adequate distribution of new antiretroviral drugs in genital compartments is essential in order to minimize residual replication in reservoirs [2, 3] and to ensure that HIV cannot be transmitted by PWH with an undetectable plasma viral load.

Our aim in this study was to evaluate the pharmacokinetic profile of the new nonnucleoside reverse transcriptase inhibitor (NNRTI) doravirine (DOR) [6] in semen and cervicovaginal fluid (CVF). We also evaluated the ability of DOR plus emtricitabine/tenofovir alafenamide (FTC/TAF) to maintain suppression of HIV-1 RNA in these compartments.

METHODS

We performed a prospective, single-arm, open-label study at the Bellvitge University Hospital, Barcelona, Spain, between February 2020 and September 2020. Eligible participants were cisgender male (n = 15) and cisgender female adults (n = 15) with HIV on stable ART (≥3 months) consisting of FTC/TAF, FTC/tenofovir disoproxil fumarate, or abacavir/lamivudine plus an NNRTI, a boosted protease inhibitor, or an integrase strand transfer inhibitor (INSTI) and blood plasma (BP) HIV-1 RNA <40 copies/mL for ≥6 months. Evidence of primary resistance or a history of virologic failure to any of the study drugs, severe liver disease (Child-Pugh class C), an estimated glomerular filtration rate <50 mL/min, pregnancy or breastfeeding, an active opportunistic infection, or malignancy were considered exclusion criteria. At baseline, ART was switched to DOR 100 mg (Pifeltro) in combination with FTC/TAF 200/25 mg (Descovy) once daily.

Our objectives for this study were to determine total and protein-unbound DOR concentrations in seminal plasma (SP) and CVF and to evaluate suppression of HIV-1 RNA in these genital fluids 8 weeks after switching to DOR + FTC/TAF.

HIV-1 RNA in BP was measured at baseline, week 4, and week 8. HIV-1 RNA was evaluated in paired SP or CVF and BP samples at baseline and week 8. DOR concentrations were determined in paired genital and BP samples at week 8. Samples were collected at the end of the dosing interval (24 hours after the dose ± 1 hour and before the following dose [C_{24}]), and participants were asked to abstain from sexual activity for at least 72 hours (males) or 24 hours (females). Sample collection and processing are described in the Supplementary Material.

Screening for sexually transmitted infections (STIs) was performed at baseline, and all clinical events and drug-related adverse events were recorded at each visit.

Samples were processed within 2 hours of collection and stored at −80°C until analysis. HIV-1 RNA was determined in BP, SP, and CVF using the Alinity m HIV-1 AMP assay (Abbott Molecular; limit of quantification, 20 copies/mL).

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Table 1. Doravirine Concentrations (C_{24h}) in Blood Plasma, Seminal Plasma, and Cervicovaginal Fluid

Males							
Total Drug C_{24h} in BP (ng/mL)	Protein-Bound Fraction in BP (%)	Protein-Unbound C_{24h} in BP (ng/mL)	Total Drug C_{24h} in SP (ng/mL)	Protein-Bound Fraction in SP (%)	Protein-Unbound C_{24h} in SP (ng/mL)	SP-to-BP Ratio Total Drug	SP-to-BP Ratio Protein-Unbound Drug
363 (77.1–566)	81.3 (58.4–86.3)	90.7 (37–172.2)	127 (31.2–272)	12.8 (0–23)	104 (27–218)	0.35 (0.40–0.48)	1.53 (0.83–2.82)
Females							
Total Drug C_{24h} in BP (ng/mL)	**Protein-Bound Fraction in BP (%)**	**Protein-Unbound C_{24h} in BP (ng/mL)**	**Total Drug C_{24h} in CVF (ng/mL)**	**Protein-Bound Fraction in CVF (%)**	**Protein-Unbound C_{24h} in CVF (ng/mL)**	**CVF to-BP Ratio Total Drug**	**CVF to-BP Ratio Protein-Unbound Drug**
479 (306–818)	82.7 (75.5–85.4)	63.6 (10.6–105.8)	505.8 (199.8–960.8)	36.6 (21–55.4)	312 (138–562)	1.06 (0.65–1.17)	3.75 (1.85–4.71)

Doravirine concentrations are shown as median and interquartile range.

Abbreviations: BP, blood plasma; C_{24h}, concentration at the end of the dosing interval and just before the next dose; CVF, cervicovaginal fluid; SP, seminal plasma.

DOR concentrations were measured in BP, SP, and CVF using liquid chromatography-tandem mass spectrometry, with a precision and accuracy of 15% (20% at the lower limit of quantification). Free and protein-bound DOR were determined using rapid equilibrium dialysis methods (procedures are described in Supplementary Material).

Quantitative variables are reported as median and range. Qualitative variables are expressed as number and percentage. All analyses were carried out using R statistical software (version 3.6.1).

This study was conducted in accordance with the Principles of Good Clinical Practice, the provisions of the Declaration of Helsinki, and the requirements of the Spanish regulatory authorities. The Bellvitge University Hospital Institutional Review Board approved the study protocol. All participants provided written informed consent.

RESULTS

Of the 30 participants enrolled, 29 (15 males and 14 females) completed all of the study procedures (1 female was lost to follow-up after the baseline visit). Baseline characteristics are described in the Supplementary Table. The median age was 41 years (range, 23–62), and the median body mass index was 25.3 kg/m^2 (18–31.9). All participants had been on stable ART for a median of 109 months (range, 16–305), and the median CD4+ T-cell count was 781 cells/µL (range, 325–1858; Supplementary Table).

Three female participants presented a positive result in the STI screening at baseline (1 for *Chlamydia trachomatis* and 2 for *Trichomonas vaginalis*), and each was prescribed appropriate antibiotic therapy.

At baseline, all participants had HIV-1 RNA <40 copies/mL in genital fluid samples. HIV-1 RNA in BP was also below the limit of detection in all individuals, except 1 female who had 52 copies/mL.

Total and protein-unbound DOR concentrations measured in paired BP and SP or CVF samples 8 weeks after switching to DOR + FTC/TAF are shown in Table 1 and Supplementary Figure 1.

The median total DOR SP-to-BP ratio was 0.35. In SP, the protein-bound percentage was 12.8% and the protein-unbound median concentration was 104 ng/mL (range, 27–218). The median total DOR CVF-to-BP ratio was 1.06. In CVF, the protein-bound fraction was 36.6%, that is, a median protein-unbound concentration of 312 ng/mL (range, 138–562).

Eight weeks after switching to DOR + FTC/TAF, all participants maintained HIV-1 RNA below the limit of detection in BP. One male had detectable HIV-1 RNA in SP (263 copies/mL) despite high DOR concentrations in this compartment (protein-unbound C_{24h} 104 ng/mL). HIV-1 RNA remained below the limit of detection in SP and CVF in all other participants.

No severe adverse effects were reported, and there were no toxicity-related treatment withdrawals.

DISCUSSION

The distribution of ART in the genital tract is conditioned by variables such as specific physicochemical properties (eg, molecular size, lipophilicity, electric charge), the affinity for plasma or genital fluid proteins, active transport through cellular membrane transporters, and the pH of the surrounding fluids and tissues [7, 8]. In this study, the distribution of DOR differed between male and female genital fluids. While the median total DOR C_{24} in CVF was comparable to the BP concentration, the median total drug C_{24} in SP accounts for 35% of the BP concentration.

Since protein binding usually differs between BP and other compartments, it is important to assess protein-unbound concentrations (the active drug fraction) in order to understand the potential activity of antiretroviral drugs in these compartments [9]. In this study, differences in protein binding were observed between SP and CVF. Protein binding was substantially lower in both genital fluids than in BP, and the median free DOR fraction was higher in SP than in CVF (87.2% vs 63.4%, respectively). Therefore, the median protein-unbound DOR concentrations in SP and CFV were, respectively, 20.4-fold and 61.2-fold above the half maximal effective concentration (EC_{50}) for wild-type HIV-1 (5.1 ng/mL). Higher drug distribution in CVF compared with SP has been observed with other antiretroviral from different classes [10–13].

Protein binding in genital fluids depends on the drug's characteristics. While most efavirenz concentrations in SP are protein-bound, comparable to BP [12, 13], higher protein-free concentrations have been observed in genital fluids compared with BP with other NNRTIs [11] and in drugs from other classes such as the INSTIs bictegravir and dolutegravir [10, 14], similar to what we observed with DOR. Regarding the drugs combined with DOR, high exposure to FTC in the genital tract has been reported in previous studies [15, 16]. Intracellular tenofovir diphosphate concentrations in semen achieved with TAF are similar to those observed with tenofovir disoproxil fumarate [17]. In contrast, lower tenofovir diphosphate concentrations were observed in vaginal tissue with TAF than with tenofovir disoproxil fumarate [18].

In this study, all participants had HIV-1 RNA <40 copies/mL in genital fluid samples at baseline, and all but 1 male also maintained HIV-1 RNA below the limit of detection 8 weeks after switching to DOR plus FTC/TAF. In this participant, HIV-1 RNA in SP at week 8 was 263 copies/mL. Interestingly, he reported good adherence, the DOR concentration in SP was markedly above the EC_{50}, and the HIV-1 RNA in BP was below the limit of detection. HIV shedding in genital fluids despite viral suppression in BP has been reported in PWH on long-term ART [19, 20] and can be partially explained by autonomous HIV replication from locally infected cells [1–3]. The presence of an STI or local inflammation has been associated with shedding of HIV in the genital tract [20]. Even though an STI could not be ruled out by microbiologic tests, this individual did not report symptoms suggesting an active infection.

We have no direct information on exposure to DOR at different anatomical sites within the genital tract or on HIV-1 RNA production by long-standing infected cells. Nonetheless, drug concentrations and HIV-1 RNA in genital fluids are widely used as surrogate markers to assess antiretroviral exposure and viral suppression in the genital tract [3, 7].

In summary, despite differences in DOR distribution and protein-binding in SP and CVF, DOR concentrations in both SP and CVF highly exceeded the EC_{50} for wild-type HIV-1. DOR + FTC/FTC maintained HIV-1 RNA suppression in these compartments in most individuals.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. A. I., J. T., and D. P. designed the study. S. S., A. I., J. M. T., M. S., and P. D. recruited participants. S. S., A. I., and S. M. conducted the study visits. I. S. and J. N. processed the samples. J. N. performed the microbiological procedures. M. L. C. and B. V. H. performed liquid chromatography-tandem mass spectrometry to measure doravirine concentrations in blood plasma, seminal plasma, and cervicovaginal fluid. M. L. C. and A. D. M. K. oversaw the bioanalytical procedures. S. M. assisted in data collection and study coordination. A. I. performed the statistical analysis. S. S., A. I., J. M. T., and D. P. analyzed and interpreted the results. S. S. and A. I. drafted the manuscript, and J. N., M. L. C., J. M. T., M. S., A. D. M. K., and D. P. reviewed it. All authors revised the manuscript for important intellectual content and contributed to the final version.

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